REMARKS

Following entry of the foregoing amendments, claims 1, 15-17, 20, 22, 23, 27, 28, and 36 constitute the pending claims in the present application. As the amendments presented in the previous Final Office Action Response (filed March 20, 2003) have not been entered, the claims and amendments presented herein are relative to the claims present in the response filed on September 27, 2002. Thus, please disregard the claims and amendments presented in the previous Final Office Action Response.

Applicants have presented herein amendments for the Examiner's consideration. Applicants have herein cancelled the nonelected claims 2-24, 18, 19, 24-25, and 29-35. Applicants have amended claims 1, 27, and 28 by replacing the phrase "unwanted activation of a *hedgehog-patched* pathway" with "unwanted hair growth or unwanted cell proliferation." Applicants have amended claim 36 by replacing the phrase "activation of the hedgehog pathway" with the phase "unwanted proliferation." Applicants have further amended claim 36 by replacing the term "patient" with the term "animal." Applicants have removed the phrase "in a sufficient amount to reduce the unwanted activation of the *hedgehog-patched* pathway in a cell of the animal" from claims 1, 27, and 28. Applicants have added the phrase "an effective amount of a" the phrase "purified organic molecule" in claims 1, 27, and 28. Applicants have changed the preamble to claims 15-17 to "The method of claim 1." Applicants have cancelled claim 21. Applicants have added new claims 37-40. Support for these claims can be found on pages 33-42 of the specification. Applicants assert that the aforementioned cancellation and amendments have been submitted solely to expedite prosecution. Applicants reserve the right to pursue the claims in their unamended forms, or claims with substantial similarity thereto, at a later date. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action. Applicants respectfully request reconsideration in view of the following remarks.

1. Claims 1, 15-17, 20-23, 27, 28, and 36 are rejected under 35 U.S.C. 112, first paragraph. Notwithstanding Applicants' arguments in their response mailed September 27, 2002, the Office Action stated that the rejection is maintained because one of ordinary skill in the art could not practice the invention without undue experimentation. The Office Action stated that "in order to

practice the claimed invention commensurate in scope with the instant claim, the skilled artisan would first have [to] identify other compounds/molecules having a molecular weight less than 750 amu or that are hedgehog antagonist, from amongst the vast number of compounds known in the chemical art, that fall within the scope of the claimed invention. It is the examiner's position that said determination is undue."

Claims 1, 27, 28 and 36 are the independent claims in the rejected claim set. Claims 15-17 and 20-23 are dependent on claim 1, and thus are not separately discussed below. With respect to claims 1, 27, 28, and 36, Applicants respectfully traverse the rejection for reasons stated below.

Claim 1 is directed to a method for inhibiting unwanted hair growth or unwanted cell proliferation in an animal, comprising administering to the animal a composition comprising an effective amount of a purified organic molecule having a molecular weight less than 750 amu, wherein the organic molecule interacts with smoothened and lessens the severity of a hedgehog gain-of-function, patched loss-of-function, or smoothened gain-of-function phenotype. Claim 27 is directed to a method for inhibiting unwanted hair growth or unwanted cell proliferation in an animal, comprising topically administering to the animal a composition comprising an effective amount of a purified hedgehog antagonist, wherein the hedgehog antagonist is an organic molecule having a molecular weight less than 750 amu and which interacts with smoothened and lessens the severity of a hedgehog gain-of-function, patched loss-of-function, or smoothened gain-of-function phenotype. Claim 28 is directed to a method for inhibiting unwanted hair growth or unwanted cell proliferation in an animal, comprising topically administering to the animal a composition comprising an effective amount of a purified hedgehog antagonist, or prodrug form thereof which is converted to a hedgehog antagonist under physiological conditions of the host animal, wherein the hedgehog antagonist is an organic molecule which interacts with smoothened and lessens the severity of a hedgehog gain-of-function, patched loss-of-function, or smoothened gain-of-function phenotype. Finally, claim 36 is directed to a method for inhibiting unwanted cell proliferation in an animal, comprising providing a cell, treating the cell with a test compound, wherein the test compound is an organic molecule having a molecular weight less than 750 amu, detecting a decrease in the level of unwanted proliferation in the cell indicative of a hedgehog inhibitory activity of the test compound, and administering to

the animal a composition comprising the test compound having a hedgehog inhibitory activity in an amount sufficient to reduce the unwanted proliferation in a cell of the animal.

Applicants assert that independent claims 1, 27, 28, and 36, and claims dependent thereon satisfy the requirements of 35 U.S.C. 112. The MPEP enumerates 8 factors that need to be considered when determining whether there is sufficient evidence to support a determination whether any necessary experimentation is "undue". These are: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. (See MPEP 2164.01(a) reiterating factors listed in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) It should also be noted that "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (See id.)

In making a determination of undue experimentation, the Office Action misconstrued the claims, and gave undue weight to the quantity of experimentation routinely involved in any drug discovery effort. Applicants point out that the Office Action misconstrued the instantly claimed invention when it stated that "in order to practice the claimed invention commensurate in scope with the instant claim, the skilled artisan would first have [to] identify other compounds/molecules having a molecular weight less than 750 amu or that are hedgehog antagonist, from amongst the vast number of compounds known in the chemical art, that fall within the scope of the claimed invention." Applicants' claims do not have a series of steps which have to be performed one after the other. For instance, without intending to be limiting in any fashion, at the time that the instant application was filed, a skilled artisan might have used automated screening techniques to screen a large library of compounds for smoothened-interacting activity, and then selected from the positive hits, those compounds with molecular weights less than 750 amu. The library of compounds might have been synthesized combinatorially, or might have been purchased from commercial vendors who specialize in selling chemical libraries for drug discovery. (See e.g., Exhibit A: ChemBridge, a commercial vendor of chemical libraries. Note that the publication date of Exhibit A, i.e., 09/15/99, predates the priority date of the present application) The screening assays were a routine part of the

experiments needed to identify small molecules which interact with smoothened, and in this respect, the specification provides more than a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. (See Specification on page 78, line 15, to page 80, line 5 for screening assays; *See also,* Specification on page 80, line 15, for working examples of disruption of hedgehog signaling using steroid alkaloids.) The amount of screening experimentation routinely involved in drug discovery, the availability of commercial or in-house libraries of small molecules at the time the instant application was filed, the availability of automated screening techniques, and the amount of guidance Applicants provided to guide one of ordinary skill in the art to identify suitable compounds, lead to the conclusion that the threshold for undue experimentation has not been met for the instantly claimed invention. Accordingly, Applicants respectfully request reconsideration and removal of the rejection of claims 1, 27, 28, and 36, and the claims dependent thereon.

2. Claims 1, 15-17, 20-23, 27, 28, and 36 are rejected under 35 U.S.C. 112, second paragraph. Notwithstanding Applicants' arguments in their response mailed September 27, 2002, the Office Action maintained the rejections of the phrase "inhibiting the unwanted activation of a hedgehog-patched pathway." The Office Action further stated that a skilled artisan would be unable to determine the scope of the claimed invention, apart from the examples provided in the specification, because he would not know what other conditions are caused by the unwanted activation of said hedgehog-patched pathway. The Office Action also rejected the use of the term "prodrug form thereof" because the specification, while providing a definition for the term, does not set forth what compounds, under physiological conditions, are converted to said active agents of the present invention. Applicants respectfully traverse the rejection to the extent that it is maintained over the amended claims.

Applicants have amended claims 1, 27, and 28 by removing the phrase "unwanted activation of a hedgehog-patched pathway" and replacing it with the phrase "unwanted hair growth or unwanted cell proliferation". Applicants have amended claim 36 by replacing the phrase "activation of a *hedgehog-patched* pathway" with the phrase "unwanted cell proliferation." Support for these amendments is found in the specification on page 51, line 25, to page 54, line 4, and page 60, line 7, to page 61 line 23. Applicants submit that the claims as

amended are definite such that one of ordinary skill in the art would know what is encompassed by the claims.

With respect to the phrase "prodrug form thereof" in claim 28, Applicants reiterate their arguments presented in their previous response. Applicants have provided a definition for the term "prodrug" in the specification. (See Specification on page 20, ln 21-25) Information which is well known in the art need not be described in detail in the specification. (MPEP 2163) Moieties that could be attached to a therapeutic agent to achieve tissue targeting or enhanced bioavailability have been well known in the art. (See, e.g., Exhibit B: Note that the publication date of Exhibit B, i.e., 04/1999, predates the priority date of the present application) Thus, Applicants submit that the skilled artisan would not have been confused by the use of the term "prodrug" in conjunction with the inhibitors in the present claims, and the further description provided both in the specification and claims clearly indicates what types of compounds would fall within the scope of the present claims. Accordingly, Applicants respectfully request removal of the objection.

3. Claims 1, 15-17, 20, 21, 27, 28, and 36 are rejected under the judicially created doctrine of obviousness-type double patenting over claims of copending Application 09/708,974. Applicants are filing a terminal disclaimer herewith to overcome the rejection. Accordingly, Applicants respectfully request reconsideration and removal of the rejection.

4. Claims 1, 15-17, 20, 21, 27, 28, and 36 are rejected under the judicially created doctrine of obviousness-type double patenting over claims Application 09/090,622 (now U.S. Patent 6,432,970). Applicants are filing a terminal disclaimer herewith to overcome the rejection. Accordingly, Applicants respectfully request reconsideration and removal of the rejection.

5. Claims 1, 15-17, 20, 21, 27, 28, and 36 are rejected under the judicially created doctrine of obviousness-type double patenting over claims of U.S. Patent 6,288,048. Applicants submit that this rejection is no longer proper in light of the scope of the amended claims as compared with the claimed subject matter of U.S. Patent 6,288,048. In particular, Applicants submit that the subject matter of the present claims is not obvious over the method of modulating cholesterol

biosynthesis or transport claimed in the '048 patent. Accordingly, Applicants respectfully request reconsideration and removal of the rejection.

6. Claims 1, 20, 21, and 36 are rejected under 35 U.S.C. 102(b) over Gerashchenko et al. Applicants respectfully traverse the rejection to the extent it is maintained over the amended claims.

Claims 1 and 36 are the independent claims in the rejected claim set. Claims 20 and 21 are dependent on claim 1. Thus, the arguments below only address the independent claims.

Applicants assert that claims 1 and 36 as amended are not anticipated by Gerashchenko et al. Specifically, Gerashchenko et al only teach using jervine and its derivatives as an anti-inflammatory agent, wherein the agents are applied to mice paws. Gerashchenko et al. do not teach or suggest the use of a hedgehog antagonist for inhibiting unwanted cell proliferation. As such, Gerashchenko fail to teach all the elements of claim 1, and claims dependent thereon. Similarly, with respect to claim 36, Applicants assert that the claim as amended is novel over Gerashchenko et al. because Gerashchenko et al do not teach inhibiting unwanted cell proliferation. Accordingly, Applicants request reconsideration and removal of the rejection.

7. Claims 15-17 are rejected under U.S.C. 103(a) over Gerashchenko et al. Applicants traverse the rejection to the extent it is maintained over the amended claims.

In response to the rejection, Applicants reiterate the argument presented above in point 6. Additionally, Applicants point out that since topical administration of jervine derivatives as anti-inflammatory agents, as taught by Gerashchenko et al. is far removed from the indications sought to be inhibited in the present claims, one of ordinary skill in the art would not have had any reasonable expectation of success that jervine or its derivatives would be effective for their presently claimed uses. Accordingly, Applicants respectfully request reconsideration and removal of the rejection.

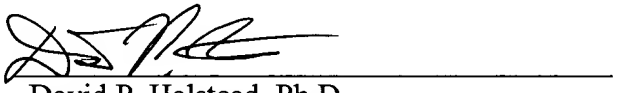
8. The Advisory Action noted that the new claims presented in the previously filed Final Office Action Response were not entered because they did not narrow the scope of the claimed compound, and were directed to non-elected subject matter. Applicants have herein presented new claims (37-40) which correspond to the elected subject matter. These new claims are

dependent on claims 1, 27, 28, or 36, and do not incorporate nonelected subject matter. Furthermore, these new claims place a structural limitation on the independent claims. Accordingly, Applicants respectfully request that these claims be entered.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945.** If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

Respectfully Submitted,



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Date: July 21, 2003

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